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(54) Title: TOPICAL VASODILATORY GEL COMPOSITION AND METHODS OF USE AND PRODUCTION

(57) Abstract

The present invention relates to a novel composition comprising a vasodilatory gel useful for topical application for stimulating blood flow, for visualizing blood vessels, for the treatment of anorgasmia, and for the treatment of impotence and other forms of vascular insufficiency, a method for making this vasodilatory gel, and a method for using this composition for stimulating blood flow, for visualizing blood vessels, for the treatment of anorgasmia, and for the treatment of impotence and other forms of vascular insufficiency. The preferred vasodilatory substance in the vasodilatory gel is nitroglycerin.

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5 TOPICAL VASODILATORY GEL COMPOSITION AND METHODS OF USE AND PRODUCTION

TECHNICAL FIELD

The present invention relates to the field of pharmacology and, in particular, 10 relates to a vasodilatory gel useful for topical application for the treatment of vascular insufficiency, a method for making the vasodilatory gel, and a method for using the vasodilatory gel for stimulating blood flow, and for the treatment of vascular insufficiency. The present invention includes use of nitroglycerin as the vasodilatory substance in the vasodilatory gel.

15

BACKGROUND OF THE INVENTION

Vascular insufficiency may be related to a variety of systems including but not limited to the nervous, endocrine, and cardiovascular systems. Vascular insufficiency affects many different functions including sexual arousal and attainment of orgasm. 20 Vascular filling of the erectile tissues of the external genitalia of males and females is a critical component in causing erections of the penis and clitoris. The corpora cavernosa and corpus spongiosum fill with blood during human sexual arousal. In the female, sexual arousal includes increased vascular flow to other structures in the perineum including the bulbs of the vestibule and the labia minora. Proper vascular 25 flow to these structures is an important component of sexual arousal, sexual response, the attainment of penile and clitoral erections, and orgasm.

Impotence is a condition of vascular insufficiency in which there is inadequate filling of the erectile tissue of the penis with blood and inadequate maintenance of the blood pressure in the erectile tissue. Impotence is a condition of varied etiology 30 including vascular, neurologic, endocrine, drug, and psychogenic causes. More specifically, peripheral vascular disease, disturbances of the autonomic motor nerves and/or sensory perineal nerves, alcoholism, reproductive steroids, diabetes, arteriosclerosis, hypertension and psychic causes may be involved in the etiology of impotence and female sexual dysfunction (see McConnell *et al.*, pg. 286-288, and 35 Carr *et al.*, pg. 289-292, both in Harrison's Principles of Internal Medicine 14th edition, 1998, Fauci *et al.*, eds., McGraw-Hill Inc., New York).

As human life expectancy grows, the incidence of peripheral vascular disease, anorgasmia, and impotence in the aging population will increase. The psychological consequences of impotence and anorgasmia include depression, loneliness, feelings

of worthlessness, performance anxiety, anxiety about sexual satisfaction of the individual with impotence or anorgasmia, and also anxiety about sexual satisfaction of his or her sexual partner. In some cases, impotent men seek psychological or psychiatric treatment and are often prescribed medications which may complicate the 5 prognosis for treatment of impotence. Many times these psychological conditions cause additional medical problems that require medical intervention. An effective composition for treating impotence that is easy to apply would decrease the incidence of these negative psychological consequences and their clinical sequelae.

10 In addition to problems affecting humans, animals may also experience difficulties obtaining erections at the appropriate time for reproduction of the species. For some animals, such as horses or cattle bred for superior genetic capabilities, the inability to obtain erections sometimes necessitates the use of electrical stimulators. Animals such as stud horses and stud cattle would benefit from methods and compositions to induce erections that do not require the use of electrical stimulators.

15 Other attempts to treat impotence include injection of papaverine, alprostadiol, phentolamine or other drugs into the corpora cavernosa of the penis (Roy *et al.*, Spinal Cord 35:99-103, 1997). While this technique is somewhat effective, the prospect of repeatedly injecting drugs into the penis is not appealing to many individuals and is associated with increased risk of infection, hematoma formation, 20 and development of scar tissue.

25 Mechanical prostheses have been implanted into the corpora cavernosa of the penis to achieve an acceptable degree of rigidity however these devices sometimes break through the skin of the penis. Other devices are based on application of vacuum to the penis with the concomitant use of rubber bands or rings to block outflow of blood from the penis. This approach is sometimes painful for the male and may produce petechial hemorrhages. This treatment may also be unattractive and uncomfortable for the sexual partner.

30 Other treatment modalities for impotence include intraurethral administration of prostaglandin E and other substances. Intraurethral application of vasodilatory substances is a mode of administration that is unappealing and uncomfortable to many men and also cumbersome in the period preceding intercourse. Furthermore, intraurethral administration can irritate the epithelium of the penile urethra and cause infection.

35 Previous attempts to increase vascular flow for cardiac problems or impotence have involved application of vasodilatory substances in the form of creams, ointments, plasters, patches, and pastes (Owen *et al.* J. Urol. 141:546-548, 1989; Heaton *et al.*, J. Urol. 143:729-731, 1990). Some of these treatments have involved

the use of nitroglycerin and related molecules. All of these methods are fraught with specific disadvantages.

Patches containing vasodilatory substances such as nitroglycerin are known in the prior art for the treatment of angina pectoris and other cardiac symptoms. These 5 patches are known by names such as TRANSDERM-NITRO® (CIBA-Geigy Corp.), DEPONIT® (Schwarz-Pharma), NITRO-DUR® (Key Pharmaceuticals, Inc.), and NITRODISC® (Roberts Pharmaceutical Corp.). These products generally contain nitroglycerin in a polymer matrix with lactose, plasticizer, resinous cross-linking agents, silicon dioxide, penetrants such as polyethylene glycol or isopropyl palmitate, 10 adhesive and other substances designed for prolonged time release characteristics. These patches are designed for long term treatment and are not configured to fit the penile shaft or to rapidly induce erections. Long term treatment with patches can also result in tolerance to the effects of nitroglycerin. Rubber bands are sometimes employed to maintain contact of the patch with the base of the penis (Roy *et al.*, 15 Spinal Cord 35:99-103, 1997). Due to the design of these patches and the differences in the length and circumference of the flaccid penis, application of such patches is impractical, cumbersome and sometimes impossible.

What is needed for treatment of impotence is not a patch or other object designed for long term drug administration, but rather a rapid onset of vasodilatory 20 response without the need to wear a patch on the penis which would be impractical and unappealing to the sexual partner.

Some pastes have incorporated dextrose particles, thereby producing a gritty, abrasive quality to the paste. Such abrasive qualities would not be desirable for application to the penis. In addition, pastes leave an undesirable residue which 25 increases exposure of the sexual partner to the paste and vasodilatory substance.

Nitroglycerin is also available in an ointment (NITRO-BID® Marion Merrell Dow Inc.), in a base of lactose containing 2% nitroglycerin, white petrolatum and lanolin. Another nitroglycerin ointment is NITROL® (Savage Laboratories) also in a base of lactose containing 2% nitroglycerin, white petrolatum and lanolin. These 30 ointments contain a petrolatum base which leaves a residue on the skin and must be removed. Use of a petrolatum based nitroglycerin ointment, which leaves a residue on the skin of the penis, would increase the exposure of the sexual partner to nitroglycerin by absorption through the mucosa of the vaginal walls.

What is also needed is a composition which may be used to stimulate blood 35 flow to the external genitalia of females in order to increase sexual arousal and the potential for orgasm. Topical application of such a composition to the external genitalia would facilitate the potential for sexual arousal and subsequent orgasm by

increasing blood flow to the perineum, including the labia minora, clitoris, and vestibule of the vagina.

Peripheral vascular disease and other problems associated with peripheral blood vessels that result in vascular insufficiency may be caused by numerous factors.

5 Some of these causes include, but are not limited to the following; diabetes, vitamin deficiency, disorders of the autonomic nervous system, smoking, drugs, especially vasoconstricting drugs, nicotine, low temperature, alcoholism, acute ischemia, atherosclerosis, phlebitis, thrombophlebitis, cardiac malfunction, trauma, obesity, Raynaud's disease, thromboangiitis obliterans (Buerger's disease) and others.

10 Peripheral vascular disease and other problems associated with peripheral blood vessels that result in vascular insufficiency cause difficulty in visualizing blood vessels. The ability to see peripheral blood vessels is needed for several reasons, including but not limited to the following: insertion of needles; insertion of catheters, such as intraarterial and intravenous catheters for removal of blood, for administration 15 of nutrients, fluids, blood or components of blood, electrolytes and pharmaceutical compositions; for insertion of angioplasty devices, stents, intravenous feeding tubes, intravenous and intraarterial probes for measurement of blood pressure and blood gases; and probes for visualization of arteries and veins in angiographic procedures.

20 In emergency situations, difficulties encountered in the visualization of a patient's blood vessels waste valuable minutes that could make the difference between life and death. Sometimes the problems encountered in obtaining access to peripheral blood vessels force health care workers to access more centrally located veins such as the jugular, femoral, brachial or subclavian veins. Some devices, such as passports, are inserted using sophisticated invasive radiological procedures to access the vascular 25 system. These procedures are more difficult to perform, are more expensive and have a higher associated risk.

30 Accordingly, what is needed is a vasodilatory composition that is convenient to use topically and is effective for rapidly increasing blood flow. What is also needed is a topical vasodilatory composition that is easy to apply, is rapidly absorbed, and does not leave a residue like creams, pastes and ointments. What is also needed is a topical vasodilatory composition for stimulating blood flow to the external genitalia of humans and animals. Also needed is a method for making this topical vasodilatory composition. In addition, what is needed is a method for using this topical vasodilatory composition for treatment of vascular insufficiency, impotence, and 35 problems associated with sexual arousal and orgasm in animals and humans.

SUMMARY OF THE INVENTION

The present invention solves the problems described above by providing a composition comprising a vasodilatory gel useful for topical application to stimulate blood flow, a method for making the vasodilatory gel, and a method for using the
5 vasodilatory gel.

The present invention also provides a method for making the vasodilatory gel of the present invention, including a vasodilatory gel containing nitroglycerin.

In addition, the present invention provides a method for rapidly stimulating blood flow by topically applying the vasodilatory gel of the present invention.

10 Specifically, the present invention provides a method for treating vascular insufficiency through topical application of the vasodilatory gel.

Most particularly, the present invention involves topical application of the vasodilatory gel.

15 The vasodilatory gel of the present invention may be used for the treatment of vascular insufficiency associated with conditions including, but not limited to the following: impotence; problems with sexual arousal; anorgasmia; frostbite; diabetes; vitamin deficiency; disorders of the autonomic nervous system; smoking; drugs, especially vasoconstricting drugs; nicotine; low temperature; alcoholism; acute ischemia; atherosclerosis; phlebitis; thrombophlebitis; cardiac malfunction; trauma; 20 obesity; Raynaud's disease; thromboangiitis obliterans (Buerger's disease); and stimulation of wound healing such as ulcer wounds by increasing blood flow; by topically applying the gel to an affected area of the skin. It is to be understood that the vasodilatory gel of the present invention may be topically applied to humans and animals who do not exhibit vascular insufficiency, as well as to humans and animals
25 who do exhibit vascular insufficiency.

30 The vasodilatory gel of the present invention may also be topically applied to enlarge blood vessels for a variety of purposes, including but not limited to, obtaining blood samples, introducing substances such as drugs, nutrients, and electrolytes into the bloodstream, inserting an intraarterial or intravenous catheter, inserting stents, inserting needles, inserting angioplasty devices, inserting devices for use in imaging of vessels and other organs, such as introduction of dyes, contrast media, or labeled compositions including radiolabeled compositions, inserting probes for radiographic visualization and localization, and inserting devices which monitor blood pressure, blood chemistry, hematocrit and blood gas content.

35 The vasodilatory gel composition of the present invention is very effectively absorbed into the skin. This superior absorption permits the use of lower concentrations of the vasodilatory substance in the gel. Furthermore, the vasodilatory composition does not leave a residue on the skin, thereby avoiding problems

associated with the use of creams, ointments, pastes, and other compositions found in the prior art.

Accordingly, an object of the present invention is to provide a vasodilatory gel which can be topically applied to increase blood flow.

5 Another object of the present invention is to provide a method for making this topical vasodilatory gel.

Yet another object of the present invention is to provide a method for using the vasodilatory gel to treat vascular insufficiency.

10 Still another object of the present invention is to provide a method for using the vasodilatory gel to increase blood flow.

A feature of the present invention is that topical application of the vasodilatory gel of the present invention rapidly increases vascular flow and facilitates visualization of blood vessels and access to blood vessels.

15 An advantage of the present invention is that topical vasodilation of the vasodilatory gel of the present invention facilitates access of health care professionals and veterinarians to the vascular system.

A further specific object of the present invention is to provide a topical vasodilatory gel which effectively increases vascular flow to the penis, thereby causing erections.

20 Another specific object of the present invention is to provide a method for using this topical vasodilatory gel for treating impotence.

Another advantage of the present invention is that topical application of the vasodilatory gel of the present invention to the penis of humans and animals, stimulates blood flow and causes erections, and is therefore useful for the treatment of impotence.

25 Another specific object of the present invention is to provide a method for using this topical vasodilatory gel for increasing vascular flow to the female external genitalia, thereby facilitating sexual arousal and the potential for attainment of orgasm.

30 Yet another specific object of the present invention is to provide a method for using this topical vasodilatory gel for treating anorgasmia.

Other advantages of the present invention are that topical application of the vasodilatory gel of the present invention to the external genitalia of female humans and animals stimulates blood flow to the erectile tissues, causes clitoral erections, facilitates sexual arousal and is therefore useful for the treatment of anorgasmia.

35 An advantage of the present invention is that the vasodilatory substance is rapidly and efficiently absorbed into the skin from the topical vasodilatory gel leaving little or no residual gel on the skin.

A specific object of the present invention is to provide compositions comprising topical vasodilatory gels containing nitroglycerin, alone, or on combination with one or more additional vasodilatory substances, and a method for making these compositions.

5 These and other objects, features and advantages of the present invention will become apparent after a review of the following detailed description of the disclosed embodiments, and the appended drawings and claims.

BRIEF DESCRIPTION OF THE FIGURES

10 Figure 1 is a graph comparing the average cumulative permeation of nitroglycerin through cadaver skin ($\mu\text{g}/\text{cm}^2$) over a period of 24 hours following application to the skin of the nitroglycerin-containing gel described herein (solid circle-Formulation E) and a nitroglycerin-containing, commercially available product (solid square-Fougera ointment).

15

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a composition comprising a vasodilatory gel useful for topical administration of vasodilatory substances, a method for making this composition, and a method for using this composition. Preferably, the vasodilatory 20 substance contains nitroglycerin. The topical nitroglycerin gel composition preferably exhibits favorable penetration properties resulting in favorable cutaneous absorption of the active ingredient and leaves little or no gel residue on the skin. Application of the nitroglycerin gel composition may be useful for treating a variety of conditions related to vascular insufficiency wherein increased vascular flow is desired, such as 25 poor cutaneous vascular flow, impotence, and anorgasmia.

The term "impotence" is used herein to mean an inability to achieve or sustain an erection of the penis.

The term "anorgasmia" is used herein to mean failure to experience orgasm.

30 The term "vasodilatory substance" is used herein to mean any compound which causes dilation of vessels, either directly or indirectly. Vasodilatory substances include vasoactive peptides such as vasoactive intestinal polypeptide, calcitonin gene-related peptide, neuropeptide Y, atrial natriuretic peptide, endothelin, and analogs and fragments thereof, including receptor agonists and antagonists. Vasodilatory substances include substances which stimulate nitric oxide synthase, the enzyme 35 responsible for nitric oxide production. Vasodilatory substances also include catecholaminergic agents, including but not limited to norepinephrine, epinephrine, dopamine, alpha adrenergic agents and beta adrenergic agents and analogs thereof. Alpha adrenergic antagonists include, but are not limited to, phentolamine and

yohimbine and analogs thereof. Beta adrenergic antagonists include, but are not limited to, propranolol, timolol, metoprolol, and atenolol and analogs thereof. Other vasodilatory substances include prostaglandins, including but not limited to prostaglandin E (PGE) and analogs thereof. Vasodilatory substances also include 5 papaverine, ergot derivatives, nicotinic acid, and nicotinyl alcohol, and analogs thereof. Vasodilatory substances also include substances referred to by those skilled in the art as nitric oxide generators which produce nitric oxide, stimulate production of nitric oxide or mimic the effect of nitric oxide generators, and analogs thereof. A preferred vasodilatory substance is nitroglycerin.

10 The term "nitric oxide generators", as used herein, means molecules which produce nitric oxide, stimulate production of nitric oxide or mimic the effect of nitric oxide generators. Such stimulation of nitric oxide production includes stimulators of the enzyme nitric oxide synthase, and nitric oxide donors. Such compounds include, but are not limited to, nitroglycerin (glyceryl trinitrate), nitroprusside, amyl nitrite, 15 sodium nitrite, pentaerythritol tetranitrate, isosorbide dinitrate, mannitol hexanitrate, and triethanolamine trinitrate biphosphate, L-arginine (free base), and dephostatin (diethylamine NONOate) and analogs thereof.

The term "gel" is used herein to mean a composition which is rapidly absorbed through the skin and leaves little or no oily or greasy residue.

20 The term "topical application" is employed to mean application of the vasodilatory compositions of the present invention to the skin. Topical application may be accomplished through means known to one of ordinary skill in the art. Such means include but are not limited to the following: manual application through the use of a gloved or non-gloved hand; application through the use of swabs, wipes, pads, 25 bandages, and sticks; and spray application. The vasodilatory gel of the present invention may also be applied topically through application to the penis of a condom containing the vasodilatory gel.

The term "animal" is used herein to mean humans and non-human animals of 30 both sexes.

The present invention also includes the combination of multiple vasodilatory substances into the vasodilatory gel composition. For example, a nitric oxide generator may be combined with one or more additional vasodilatory substances in the vasodilatory gel composition. In one embodiment, nitroglycerin may be combined with other vasodilatory substances in the vasodilatory gel composition.

35 It is to be understood that the present invention is not limited to the use of gels, and that the vasodilatory composition of the present invention may be used in other forms such as sticks, sprays, liquids, creams, and ointments.

Vasodilatory Gel Composition

In a preferred embodiment, the vasodilatory gel composition described herein contains one or more vasodilatory substances, a polymer, a penetrant or solvent, and a neutralizing agent. Preferably, the gel contains about 0.5% to 20%, more preferably 1% to 10%, and most preferably 1.5% to 4% (weight/weight) of the vasodilatory substance. Unless otherwise indicated, expressions of percentages are on a weight/weight basis throughout the present application. Preferably, the gel contains about 0.15% to 15%, more preferably 0.5% to 10%, and most preferably 1% to 5% of the polymer. Preferably, the gel contains about 75% to 99%, more preferably 80% to 97%, and most preferably 90% to 96% of the solvent or penetrant. Preferably, the gel contains about 0.01% to 0.5%, more preferably 0.05% to 0.4%, and most preferably 0.1% to 0.3% of the neutralizing agent.

In one embodiment, the vasodilatory substance is combined with an acrylic polymer, preferably carboxy polymethylene, a solvent or penetrant, preferably propylene glycol, and a neutralizing agent. Neutralizing agents include, but are not limited to tris (hydroxymethyl) aminomethane, sodium hydroxide (NaOH), and sodium phosphate, including monobasic, dibasic and tribasic forms of sodium phosphate. A preferred neutralizing agent is tris (hydroxymethyl) aminomethane. These ingredients are described in further detail below.

A preferred embodiment is a vasodilatory gel composition comprising about 0.5% to 20% of nitroglycerin, 75% to 99% propylene glycol, 0.15% to 15% carboxy polymethylene, and about 0.01% to 0.5% of tris (hydroxymethyl) aminomethane. More preferred is a vasodilatory gel composition comprising a gel containing about 1% to 10% of nitroglycerin, about 80% to 97% of propylene glycol, about 0.5% to 10% of carboxy polymethylene and about 0.05% to 0.4% of tris (hydroxymethyl) aminomethane. Most preferred is a vasodilatory gel composition comprising a gel containing about 1.5% to 4% of nitroglycerin, about 90% to 96% of propylene glycol, about 1% to 5% of carboxy polymethylene, and about 0.1% to 0.3% of tris (hydroxymethyl) aminomethane. These compositions are all compatible with topical application.

It is to be understood that preservatives, antiseptics, bacteriostats, anti-viral compounds, contraceptives, stabilizers and antioxidants well known to those of ordinary skill in the art can be used in the vasodilatory composition. In addition, compositions and agents known by one of ordinary skill in the art to be useful in preventing sexually transmitted disease or other infectious diseases, including blood borne infectious diseases, may be combined with the vasodilatory composition of the present invention. It is also to be understood that various anti-fungals, anti-

microbials, antiseptics, anesthetics, analgesics, tactile sensitizers, moisturizers, lubricants, colors, flavors, fragrances and assorted scents known to one of skill in the art may be added to the vasodilatory composition.

5 *Method of Making a Vasodilatory Gel Composition*

The vasodilatory gel is produced in the following manner. The vasodilatory substance is dissolved in an appropriate solvent. The preferred solvent is propylene glycol. It is to be understood that different vasodilatory substances require different solvation conditions. One of skill in the art would be able to determine which solvent or solvents are useful for solubilizing different vasodilatory substances. Accordingly, other solvents and penetrants besides propylene glycol may be employed. It is to be understood that some chemicals, such as propylene glycol, act as both a solvent and penetrant. In one embodiment, the vasodilatory substance is the nitric oxide generator nitroglycerin in powdered form. This nitroglycerin powder is added to the solvent and penetrant, propylene glycol, with slow sifting, such that the powder is sprinkled as discrete particles into a vortex of propylene glycol created by a mixer. The concentration of nitroglycerin is an amount of about 1% to 30% of nitroglycerin to propylene glycol. Stirring or mixing is done in a manner to avoid entrapment of air bubbles by adjusting the stirring or mixing speed. This step may be performed at room temperature although temperatures of from approximately 13° C to 33° C may be employed. The mixer is a vertical shaft mixer operating at less than about 500 rpm to create a vortex, although other mixers and stirrers may be employed. The mixing is sufficient to thoroughly dissolve the nitroglycerin in propylene glycol. A preferred mixture of nitroglycerin in propylene glycol is about 1% to 20%. A more preferred mixture of nitroglycerin in propylene glycol is about 3% to 15%. Another more preferred mixture of nitroglycerin in propylene glycol is about 4% to 12%.

A polymer, such as an acrylic polymer, is added with slow sifting into a vortex of penetrant, such as propylene glycol, using a stirrer or mixer. Acrylic polymers which may be used in the practice of the present invention include, but are not limited to carboxy polymethylene. Carboxy polymethylene is also known CARBOPOL® and carbomer, and is manufactured by B. F. Goodrich Specialty Chemicals. Acceptable carboxy polymethylene for use in the present invention includes, but is not limited to carboxy polymethylene known as CARBOPOL® 934P NF, CARBOPOL® 974P NF, and CARBOPOL® 980 NF. The amount of acrylic polymer as a percent of the total weight of the vasodilatory composition is about 0.15% to 15%, preferably 0.5% to 10%, more preferably from 1.0% to 5%. In one preferred embodiment, carboxy polymethylene is used as the acrylic polymer at a final concentration of 1.5%. Stirring and mixing are performed in a manner to avoid formation or

entrapment of air bubbles. This step is performed at room temperature although temperatures of from approximately 13° C to 33° C may be employed. After initial dissolution of carboxy polymethylene in a small amount of propylene glycol, the carboxy polymethylene is added to the vortex of the mixture of nitroglycerin in propylene glycol created by a mixer. Addition of carboxy polymethylene in this manner facilitates proper and complete wetting and avoids lumping. Stirring or mixing is done in a manner to avoid entrapment of air bubbles. The mixer is a vertical shaft mixer operating at less than about 500 rpm to create a vortex, although other mixers, such as impeller mixers and stirrers may be employed. The mixing is sufficient to thoroughly mix the carboxy polymethylene in the nitroglycerin/propylene glycol mixture. Any air bubbles present at this time are removed by reducing the speed of the mixer.

Neutralizing agents are initially dissolved in a solvent, such as propylene glycol, by heating the mixture at a temperature below approximately 60° C. Temperatures ranging from about 35° C to 60° C, preferably 40° C to 58° C, most preferably 40° C to 50° C, may be used for dissolving the neutralizing agent in the solvent. Neutralizing agents useful in the practice of the present invention include, but are not limited to tris (hydroxymethyl) aminomethane, sodium phosphate and NaOH. Tribasic sodium phosphate is a preferred form of sodium phosphate. It is to be understood that other neutralizing agents and bases may be employed and are encompassed within the scope of the present invention. Neutralizing agents are dissolved in a container separate from the container with the vasodilatory substance.

The final concentration of a neutralizing agent, such as tris (hydroxymethyl) aminomethane, in the vasodilatory composition is about 0.01% to 0.5%. A more preferred concentration is about 0.05% to 0.4% of tris (hydroxymethyl) aminomethane. A most preferred concentration of tris (hydroxymethyl) aminomethane is about 0.1% to 0.3%.

Next, the solution of neutralizing agent in propylene glycol is cooled to room temperature. This cooling step may occur gradually at room temperature or may be accelerated through the use of water jacketed tanks or other means known to one of skill in the art. At this step, air bubbles are removed from the dispersion. Next, the mixer speed is reduced and the neutralizing agent is added gradually to the mixture containing the vasodilatory substance and polymer, resulting in gel formation. Although gel formation may begin at a pH of approximately 6, the neutralizing agent is added until a pH of approximately 7.2 is obtained so that topical application of the gel occurs at relatively neutral pH conditions.

When NaOH is used as the neutralizing agent, a sufficient amount of NaOH is added to attain a final pH of approximately 6.5. Final pH values of from about 6.5 to

7.2 are generally acceptable in the formation of the vasodilatory composition of the present invention.

Method of Using the Vasodilatory Gel Composition

5 The vasodilatory gel composition of the present invention is topically applied to the skin in amounts such that at least about 2 mg of active vasodilatory substance or substances is applied. Various means may be used for application such as pads, wipes, tubes, cotton swabs, plastic or wooden applicators, aerosols such as sprays, applicator cans or bottles, gauze, gloved hand, digital glove and condom. In one
10 10 preferred use, the vasodilatory gel composition is applied as one would apply a lubricant to the penile skin on the shaft and/or on the glans.

Topical application of the vasodilatory gel composition of the present invention to the penis for the treatment of impotence can be used to enhance fertility by producing erections of sufficient strength and duration to achieve vaginal penetration
15 15 and ejaculation. Topical application of the vasodilatory gel facilitates sexual arousal and increases the chances for attainment of orgasm and ejaculation. When an erection is desired for heterosexual intercourse without conception, a condom containing the vasodilatory gel may be worn throughout intercourse.

Topical application of the vasodilatory gel composition of the present invention to external genitalia of women increases blood flow, facilitates sexual arousal and increases the chances for attainment of orgasm. Accordingly, this topical application may be used as a treatment for anorgasmia. Since topical application of the vasodilatory gel composition facilitates sexual arousal, it may be used to increase the opportunity for sexual intercourse and increase sexual satisfaction. Another potential
25 25 benefit of topically applying the vasodilatory gel composition is that fertility may be enhanced by increasing the frequency of heterosexual intercourse.

The vasodilatory gel is rapidly absorbed and leaves little or no residue. Soon after application, blood flow increases. When the vasodilatory gel composition is applied to the skin of the penis, absorption rapidly occurs and tumescence increases
30 30 resulting in an erection. It is to be understood that the vasodilatory gel composition of the present invention may be topically applied to the penis to stimulate blood flow and produce erections in individuals who are not impotent. It is also to be understood that the vasodilatory gel composition of the present invention may be topically applied to the external genitalia of females to stimulate blood flow in individuals who have no difficulty in becoming sexually aroused or attaining orgasm.

An important aspect of the present invention is that topical application of the vasodilatory composition increases blood flow. An advantage of the present invention is that the vasodilatory composition is rapidly and efficiently absorbed

thereby transporting the vasodilatory substance into and across the skin. An additional advantage is that little or no residue remains after the vasodilatory gel is absorbed into the skin.

An advantage of the present invention is that topical application to the skin 5 increases vascular diameter and enables visualization of blood vessels for insertion of a variety of devices, including but not limited to needles, shunts, catheters, and probes to measure blood pressure and blood oxygenation. Desirable locations for topical application of the vasodilatory composition of the present invention for the purpose of dilating vessels include, but are not limited to the following: the upper 10 extremity, including the dorsum of the hand, the wrist, forearm, antecubital fossa and arm; the neck; the lower extremity, including the foot, ankle, leg, popliteal fossa, thigh; the torso, the scalp and other sites known to one of ordinary skill in the art. It is to be understood that the vasodilatory gel of the present invention may be topically applied in order to stimulate blood flow through dilation of vessels in humans and 15 animals who do not exhibit vascular insufficiency, as well as those who do exhibit some vascular insufficiency.

The present invention is further illustrated by the following examples, which are not to be construed in any way as imposing limitations upon the scope thereof. On the contrary, it is to be clearly understood that resort may be had to various other 20 embodiments, modifications, and equivalents thereof, which, after reading the description herein, may suggest themselves to those skilled in the art without departing from the spirit of the present invention.

EXAMPLE 1

25 *Method for Preparation of a Topical Nitroglycerin Gel*

The following method was used to prepare 10 gallons of a nitroglycerin (NTG)-containing gel, which is shown in Figure 1 as Formulation E. Table 1 displays the relative amounts of ingredients used to make the nitroglycerin-containing gel.

TABLE 1

30	Composition	Amount (kg)
	Nitroglycerin/propylene glycol mixture 10% NTG in propylene glycol	7.6
	Carboxy Polymethylene (CARBOPOL® - 934P NF)	0.57
	Propylene glycol	28.31
	Neutralizing agent: Tris (hydroxymethyl) aminomethane (0.092 kg) in propylene glycol (1.428 kg)	1.520
	Total weight	38.0

Note - The total volume was slightly less than 10 gallons, since the formula was not adjusted for specific gravity (1.065 at 25°C for SDM 27, Zeneca Specialties and 1.035 at 25°C for propylene glycol).

5 Nitroglycerin was added at room temperature to propylene glycol with slow sifting, such that the nitroglycerin was sprinkled as discrete particles into a vortex of propylene glycol created by a mixer. The concentration of nitroglycerin was about 10% of nitroglycerin to propylene glycol (weight/weight%). Stirring or mixing was done in a manner to avoid entrapment of air bubbles by adjusting the stirring or mixing speed. The mixer was a vertical shaft mixer operating at less than 500 rpm to
10 create a vortex. The mixing was sufficient to thoroughly dissolve the nitroglycerin in propylene glycol. Samples of the mixture were obtained from different location in the vortex to examine the degree of solvation.

15 After initial dissolution of carboxy polymethylene (0.57 kg) in a small amount of propylene glycol, the carboxy polymethylene was added to the vortex of the mixture of nitroglycerin in propylene glycol. Carboxy polymethylene was added to achieve a final concentration in the vasodilatory gel composition of about 1.5% (weight/weight). Additional propylene glycol was added as shown in Table 1. Stirring and mixing were performed in a manner to avoid formation or entrapment of air bubbles. This step was performed at room temperature. Addition of carboxy
20 polymethylene in this manner facilitates proper and complete wetting and avoids lumping. Stirring or mixing was done in a manner to avoid entrapment of air bubbles. The mixer used was a vertical shaft mixer operating at less than 500 rpm to create a vortex. The mixing was sufficient to thoroughly mix the carboxy polymethylene in the nitroglycerin/propylene glycol mixture. Any air bubbles present
25 at this time were removed by reducing the speed of the mixer.

30 The neutralizing agent used was a 0.5 M solution of tris (hydroxymethyl) aminomethane (ANGUS Chemical Company, Buffalo Grove, IL) in propylene glycol. The tris (hydroxymethyl) aminomethane solution was prepared in a separate container from the vessel containing the nitroglycerin/propylene glycol mixture. This tris (hydroxymethyl) aminomethane solution was prepared by adding tris amino (0.092 kg) to propylene glycol (1.428 kg) and heating this mixture at 55° C to 60° C with constant stirring until the tris (hydroxymethyl) aminomethane completely dissolved in the propylene glycol.

35 The solution of tris (hydroxymethyl) aminomethane was permitted to return to room temperature before adding it to the mixture containing the nitroglycerin, propylene glycol, and carboxy polymethylene. After ensuring that there were no air bubbles in the mixture, the speed of the mixer was reduced such that no vortex was created. Next the tris (hydroxymethyl) aminomethane neutralizing agent (1.52 kg)

was added resulting in gel formation and a sudden increase in the viscosity. At this point the mixing speed was optionally increased to ensure neutralization of the entire mixture but without entrapping air or creating a vortex. A colorless to translucent gel was formed. Neutralization started to occur at a pH of about 6, and so no more than 5 the mentioned amount of neutralizing agent was added even if the final pH was not 7.4.

When the impeller mixer was used it was submerged until it was very close to the bottom of the vessel while creating the vortex. The mixer was positioned at an angle to generate a vortex which was one to one-and-one-half times the diameter of 10 the impeller. The speed was adjusted to about 1200 rpm. While not wanting to be bound by the following statement, it appears that extreme shear conditions degrade the CARBOPOL® resin molecules, resulting in a permanent loss of viscosity. Entrapped air was permitted to escape before neutralization with tris (hydroxymethyl) aminomethane.

15 While making this mixture, over-neutralization was prevented by not exceeding the amount of neutralizing agent mentioned, since that resulted in a permanent loss of viscosity. Caution must be exercised during formation of this mixture since separation of nitroglycerin from the mixture could result in the formation of an explosive substance. Furthermore, nitroglycerin may be harmful if swallowed, 20 inhaled or absorbed through skin in high concentrations.

EXAMPLE 2

Penetration Efficacy of Topically Applied Nitroglycerin Gel: Comparative Skin Permeation Study of Formulation E Gel and Fougera Ointment

25 Skin Permeation Study: Human cadaver skin was obtained from a skin/tissue bank after Institutional Review Board approval from Auburn University. The skin was obtained from healthy normal, HIV negative, hepatitis-negative donors. Skin was frozen within 12 hours of death and supplied as a piece of full thickness skin. Once received, the skin was stored at -80°C and thawed just before use. The 30 resistance of each skin piece was measured with an ohmmeter before proceeding to verify the integrity of the skin. Any piece with a resistance of less than 40 kΩ was rejected.

Franz (vertical) diffusion cells were used for the *in vitro* permeation studies. The donor half was exposed to room temperature (25° C) while the receptor half was 35 maintained at 37° C. Full thickness human cadaver skin was thawed and the epidermis was separated by a widely used method, wherein skin was heated in distilled water at 60° C for 45 seconds and then the epidermis was pulled off. Since only the gel in contact with the skin will permeate, the amount required to fully cover

the skin by spreading was determined. This amount of gel was about 75 mg and contained 1.5 mg of nitroglycerin (approximately 2% final concentration). The epidermis was placed on a piece of parafilm and 75 mg of either Formulation E gel or Fougera ointment was placed on its center. The piece of epidermis was then mounted 5 on the vertical diffusion cells after the receptor compartment was filled with 5.0 ml of 20% propylene glycol in saline. The gel or ointment was spread with a spatula so that it covered the entire area enclosed by the donor compartment. Next, the donor cell was clamped into place. Samples were taken at various time intervals and the nitroglycerin content determined using a method described below. The results of the 10 permeation experiments are presented in Figure 1 and are plotted as the cumulative amount of drug permeated as a function of time. Samples were replaced with 20% propylene glycol in saline and this was taken into consideration in the calculations.

Analysis of Nitroglycerin Content in the Samples

15 Analysis was done using an HPLC assay (USP Method) and a C18 column. The mobile phase was a combination of methanol and water (50:50) and the flow rate was 1 ml/minute. Absorbance was monitored in a spectrophotometer at 220 nm. The retention time of nitroglycerin was approximately 9 minutes. A standard curve was made by injecting different amounts of a standard solution of nitroglycerin into the 20 HPLC and analyzing peak height and area under the curve for subsequent calculations of the nitroglycerin content of transported samples.

25 The results showed both an increased rate of nitroglycerin transport as indicated by a shift to the left of the permeation curve and also a higher total transport of nitroglycerin in the vasodilatory composition of Formulation E Gel when compared to Fougera ointment. Fougera ointment contained the same nitroglycerin concentration as the sample. These results indicate that the nitroglycerin is efficiently absorbed into the skin from the topical vasodilatory gel of the present invention.

EXAMPLE 3

30 *Application of the Topical Vasodilatory Gel Containing Nitroglycerin to the Penis of a Human*

35 A male with a history of impotence topically and manually applies the vasodilatory gel containing nitroglycerin to his penis. A total nitroglycerin dose of between about 2 mg and 20 mg is applied. Following absorption of the gel, penile tumescence increases and an erection is achieved. The erection persists for a period of about 9.5 to 20 minutes. No residual gel remains on the penis after application, indicating rapid and thorough absorption into the skin.

EXAMPLE 4*Application of the Topical Vasodilatory Gel Containing Nitroglycerin to the Penis of a Human to Enhance Fertility*

5 A male with a history of impotence manually applies a condom containing the vasodilatory gel containing nitroglycerin to his penis. Following absorption of the gel, penile tumescence increases and an erection is achieved. The condom is removed. The erection persists for a period of time sufficient for vaginal penetration and ejaculation. No residual gel remains on the penis after application, indicating rapid and thorough absorption into the skin.

10

EXAMPLE 5*Application of the Topical Vasodilatory Gel Containing Nitroglycerin to the Penis of a Human*

15 A male with a history of impotence manually applies a condom containing the vasodilatory gel containing nitroglycerin to his penis. Following absorption of the gel, penile tumescence increases and an erection is achieved. The condom remains on the penis. The erection persists for a period of time sufficient for vaginal penetration and ejaculation. No residual gel remains on the penis after application, indicating rapid and thorough absorption into the skin.

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EXAMPLE 6*Application of the Topical Nitroglycerin Gel to Stimulate Blood Flow to the Foot*

25 A female with peripheral vascular insufficiency secondary to diabetes topically applies the vasodilatory gel composition containing nitroglycerin to the skin of the foot. The amount of vasodilatory gel was sufficient to contain at least 2 mg of nitroglycerin. Within seconds, she notices increased vasodilation in cutaneous vessels. The vasodilation is accompanied by a sensation of warmth in the foot.

EXAMPLE 7

30 *Application of the Topical Nitroglycerin Gel to Stimulate Blood Flow in the Upper Extremity*

35 A male with peripheral veins that can not be visualized in the antecubital fossa and the ventral surface of the wrist requires insertion of a vascular line and withdrawal of a blood sample. A health care worker applies the vasodilatory gel composition containing nitroglycerin to the skin of the antecubital fossa and/or the ventral surface of the wrist. The amount of vasodilatory gel was sufficient to contain at least 2 mg of nitroglycerin. Within seconds, increased vasodilation in cutaneous vessels renders visible the veins and arteries in these regions. The vasodilation is

sufficient to enable the health care worker to insert a needle into the vein to obtain a blood sample and also to insert a catheter.

EXAMPLE 8

5 *Emergency Application of the Topical Nitroglycerin Gel to Rapidly Stimulate Blood Flow in the Upper Extremity*

An elderly, overweight male with peripheral veins in the upper and lower extremities that can not be visualized is admitted to the emergency room in a state of shock and dehydration. Blood samples are needed to examine blood chemistry.

10 Rapid insertion of intravenous lines for administration of fluids and electrolytes is desired by the health care professionals. Rapid insertion of an intraarterial radial line is desired by the health care professionals for evaluation of pulse pressures and blood gases.

Emergency room health care professionals apply the vasodilatory gel containing nitroglycerin to the antecubital fossa, the ventral surface of the wrist and to the ankle. The amount of vasodilatory gel is sufficient to contain at least 2 mg, preferably 5 mg, of nitroglycerin at each site of application. The blood vessels in these regions dilate soon after application of the vasodilatory gel. The health care professionals then insert intravenous lines in the antecubital fossa and in the veins of the ankle, and an intraarterial line in the radial artery.

EXAMPLE 9

Application of the Topical Nitroglycerin Gel to Stimulate Blood Flow to the Female External Genitalia

25 A female applies the vasodilatory gel composition containing nitroglycerin to her external genitalia, specifically to the labia majora, labia minora and clitoris. The amount of vasodilatory gel was sufficient to contain at least 2 mg of nitroglycerin. Within seconds, she notices an increased sensation of warmth in her external genitalia secondary to increased vascular flow. These sensations are accompanied by

30 increased sexual arousal.

EXAMPLE 10

Treatment of Anorgasmia by Application of the Topical Nitroglycerin Gel to the Female External Genitalia

35 A female with a history of anorgasmia applies the vasodilatory gel composition containing nitroglycerin to her external genitalia, specifically to her labia majora, labia minora and clitoris. The amount of vasodilatory gel was sufficient to contain at least 2 mg of nitroglycerin. Within seconds, she notices an increased sensation of warmth

in her external genitalia secondary to increased vascular flow. These sensations are accompanied by increased sexual arousal. Her sensation of enhanced sexual arousal, coupled with increased tactile stimulation of the clitoris, facilitates attainment of an orgasm.

5

It should be understood, of course, that the foregoing relates only to preferred embodiments of the present invention and that numerous modifications or alterations may be made therein without departing from the spirit and the scope of the invention as set forth in the appended claims.

10

Claims

1. A composition comprising:
5 a vasodilatory substance;
 a polymer;
 a solvent; and
 a neutralizing agent.
- 10 2. The composition of Claim 1, comprising about 0.5% to 20% by weight of
 the vasodilatory substance, about 0.15% to 15% by weight of the polymer, about
 75% to 99% by weight of the solvent, and about 0.01% to 0.5% by weight of the
 neutralizing agent.
- 15 3. The composition of Claim 1, wherein the vasodilatory substance is
 nitroglycerin, the polymer is carboxy polymethylene, the solvent is propylene glycol
 and the neutralizing agent is tris (hydroxymethyl) aminomethane, sodium phosphate,
 tribasic sodium phosphate or sodium hydroxide.
- 20 4. The composition of Claim 3, comprising about 0.5% to 20% by weight of
 nitroglycerin, about 0.15% to 15% by weight of carboxy polymethylene, about 75%
 to 99% by weight of propylene glycol, and about 0.01% to 0.5% by weight of tris
 (hydroxymethyl) aminomethane.
- 25 5. The composition of Claim 3, comprising about 1% to 10% by weight of
 nitroglycerin, about 0.5% to 10% by weight of carboxy polymethylene, about 80% to
 97% by weight of propylene glycol, and about 0.05% to 0.4% by weight of tris
 (hydroxymethyl) aminomethane.
- 30 6. The composition of Claim 3, comprising about 1.5% to 4% by weight of
 nitroglycerin, about 1% to 5% by weight of carboxy polymethylene, about 90% to
 96% by weight of propylene glycol, and about 0.1% to 0.3% by weight of tris
 (hydroxymethyl) aminomethane.
- 35 7. The composition of Claim 1, wherein the vasodilatory substance comprises a
 peptide, catecholamine, prostaglandin, papaverine, ergot derivative, nicotine, nitric
 oxide generator, analogs thereof and combinations thereof.

8. The composition of Claim 7, wherein the nitric oxide generator comprises nitroglycerin, nitroprusside, amyl nitrite, sodium nitrite, pentaerythritol tetranitrate, isosorbide dinitrate, mannitol hexanitrate, triethanolamine trinitrate biphosphate, L-arginine, dephostatin, analogs thereof, and combinations thereof.

5

9. The composition of Claim 7, wherein the catecholamine comprises norepinephrine, epinephrine, dopamine, alpha adrenergic antagonists, beta adrenergic antagonists, analogs thereof, and combinations thereof.

10

10. The composition of Claim 7, wherein the peptide comprises vasoactive intestinal polypeptide, calcitonin gene-related peptide, atrial natriuretic peptide, neuropeptide Y, endothelin, analogs thereof, and combinations thereof.

15

11. The composition of Claim 1, wherein the vasodilatory substance is nitroglycerin

12. The composition of Claim 11, wherein the nitroglycerin is present in an amount of about 0.5% to 20% by weight.

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13. The composition of Claim 11, wherein the nitroglycerin is present in an amount of about 1% to 10% by weight.

14. The composition of Claim 11, wherein the nitroglycerin is present in an amount of about 1.5% to 4% by weight.

25

15. The composition of Claim 1, wherein the polymer is an acrylic polymer.

16. The composition of Claim 15, wherein the acrylic polymer is carboxy polymethylene.

30

17. The composition of Claim 16, wherein the carboxy polymethylene is present in an amount of about 0.15% to 15% by weight.

18. The composition of Claim 1, wherein the solvent is propylene glycol.

35

19. The composition of Claim 18, wherein the propylene glycol is present in an amount of about 75% to 99% by weight.

20. The composition of Claim 1, wherein the neutralizing agent is tris (hydroxymethyl) aminomethane, sodium phosphate, tribasic sodium phosphate, or sodium hydroxide.

5 21. The composition of Claim 1, wherein the neutralizing agent is tris (hydroxymethyl) aminomethane.

22. The composition of Claim 21, wherein the tris (hydroxymethyl) aminomethane is present in an amount of about 0.01% to 0.5% by weight.

10 23. A method of making the composition of Claim 1, comprising:
dissolving the vasodilatory substance in the solvent to form a first mixture;
stirring the first mixture;
mixing the polymer with the solvent to form a second mixture;
15 combining the second mixture with the first mixture to form a third mixture;
dissolving the neutralizing agent in the solvent at a temperature below about 60°C to form a fourth mixture;
cooling the fourth mixture; and
gradually adding the fourth mixture to the third mixture to form a gel.

20 24. The method of Claim 23, wherein the vasodilatory substance is nitroglycerin, the polymer is carboxy polymethylene, the solvent is propylene glycol and the neutralizing agent is tris (hydroxymethyl) aminomethane, sodium phosphate, tribasic sodium phosphate or sodium hydroxide.

25 25. The method of Claim 24, wherein the nitroglycerin is added to the propylene glycol in an amount of approximately 1% to 30% by weight.

30 26. The method of Claim 24, wherein the nitroglycerin is added to the propylene glycol in an amount of approximately 1% to 20% by weight.

27. The method of Claim 24, wherein the nitroglycerin is added to the propylene glycol in an amount of approximately 3% to 15% by weight.

35 28. The method of Claim 24, wherein the polymer is added to the propylene glycol in an amount of approximately 1% to 30% by weight.

29. The method of Claim 23, wherein the neutralizing agent is dissolved in the solvent at a temperature between about 35°C to 60°C.

30. The method of Claim 23, wherein the neutralizing agent is dissolved in the 5 solvent at a temperature between about 40°C to 58°C.

31. A method of stimulating blood flow in a human or animal comprising topical application to the human or the animal of an effective amount of the composition of Claim 1, wherein the amount is effective to dilate vessels in the human 10 or the animal.

32. A method of stimulating blood flow in a human or animal comprising topical application to the human or the animal of an effective amount of the composition of Claim 3, wherein the amount is effective to dilate vessels in the human 15 or the animal.

33. The method of Claim 31, wherein the human or animal has vascular insufficiency associated with or caused by impotence, anorgasmia, peripheral 20 vascular disease, diabetes, vitamin deficiency, disorders of the autonomic nervous system, smoking, drugs, low temperature, alcoholism, acute ischemia, atherosclerosis, phlebitis, thrombophlebitis, cardiac malfunction, trauma, obesity, Raynaud's disease, or thromboangiitis obliterans.

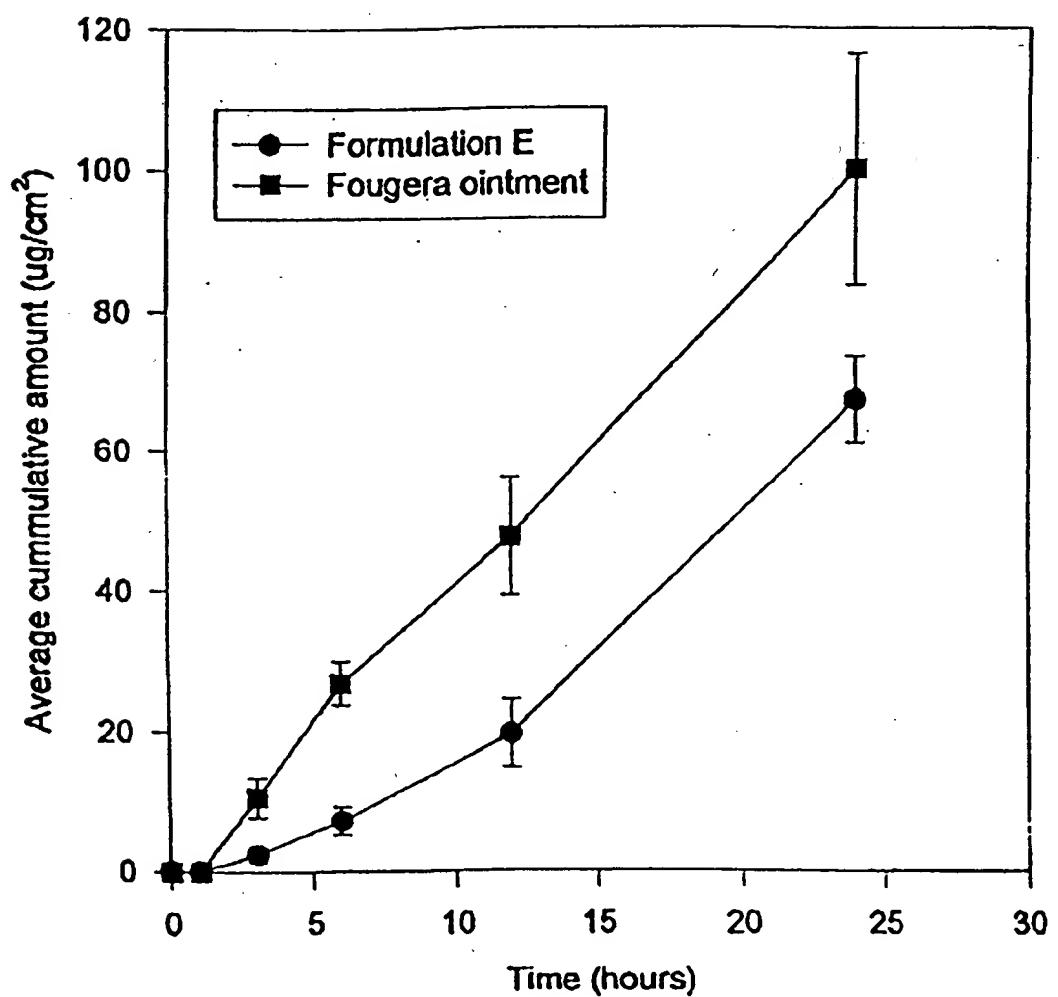
34. The method of Claim 32, wherein the human or animal has vascular 25 insufficiency associated with or caused by impotence, anorgasmia, peripheral vascular disease, diabetes, vitamin deficiency, disorders of the autonomic nervous system, smoking, drugs, low temperature, alcoholism, acute ischemia, atherosclerosis, phlebitis, thrombophlebitis, cardiac malfunction, trauma, obesity, Raynaud's disease, or thromboangiitis obliterans.

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35. The method of Claim 31, wherein the human or animal has impotence or anorgasmia.

35

36. The method of Claim 32, wherein the human or animal has impotence or anorgasmia.



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